REDUCTIVE CONDENSATION OF 4-BENZYLOXYBENZOPHENONE AND PROPIOPHENONE, AND THE ESTROGENIC ACTIVITY OF 1-BENZYLOXY-4-(1,2-DIPHENYLBUT-1-ENYL)BENZENE

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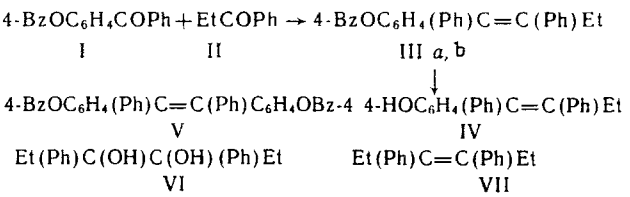
The reductive linkage of carbonyl compounds in the presence of a low-valent titanium reagent, discovered and investigated in the 1970's [9], has subsequently been used [3, 4] in the synthesis of tamoxifen, which is a highly effective drug used in oncology [2]. For this purpose, two ketones are subjected to reductive condensation, namely propiophenone and 4-hydroxybenzophenone (or its O-alkyl derivatives) [6].

We have examined the reductive linkage of 4-benzyloxybenzophenone (I) and propiophenone (II) in the presence of a low-valent titanium reagent obtained by reducing $TiCl_4$ with zinc dust. The reaction was carried out under argon or nitrogen, using a molar ratio of ketones of 1:1.

The principal reaction product is 1-benzyloxy-4-(1,2-diphenylbut-1-enyl)-benzene (III) (yields 86-87%), which is formed by the preferential cross-linking of the aromatic ketones (I) and (II). Its mass and IR spectra confirm the structure of (III), but give no information on the stereochemistry of the compounds. The PMR spectrum shows that the butene (III) is a mixture of the Z- and E-isomers, the former predominating. The PMR spectrum shows doubling of the signals for the ethyl protons (~0.9 ppm for CH_3 and ~2.45 ppm for CH_2), the methylene groups (~5 ppm) of the benzyl groups, and the signals (6.65-7.44 ppm) for the phenyl protons. The ratio of the triplet signals for the methyl groups (0.9 and 0.925 ppm) and the singlet signals for the methylene groups (4.96 and 4.98 ppm) is 5:1. The signals at higher field are attributed to the Z-isomer [7]. Crystallization of the isomer mixture gave Z-1-benzyloxy-4-(1,2-diphenyl-1-butenyl)benzene (IIIa).

The by-products formed in the reaction (V-VII) are formed by similar condensation of the ketones (I) and (II).



Compound (V) is formed by dimerization of two molecules of the ketone (I), and (VI) and (VII) by the reductive dimerization of propiophenone, the results of which have been reported [1].

Compound (V) was obtained independently in 41% yield by reductive linkage of the ketone (I) under the conditions described above. The IR and mass spectra confirm the structure proposed for (V), and its PMR spectrum shows doubled signals for the methylene groups at 4.96 and 4.98 ppm in a ratio close to 1:1.

The ketone (I) was synthesized from 4-hydroxybenzophenone by treatment with benzyl chloride in an alkaline medium [10].

Debenzylation of the butene (III) with Raney nickel in alcohol, or by boiling with a mixture of glacial acetic and hydrobromic acids, gave the known 4-(1,2-diphenylbut-1-enyl)

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TABLE 1. Estrogenic and Antiestrogenic Activity of (Z)- and (Z/E)-1-benzyloxy-4-(1,2-diphenylbut-1-enyl)benzene (IIIa, IIIb)

Group No.*	Compound and dose, mg/kg		Mass of uterus, mg per 100 g body weight**
1	—	—	91,3±13,1
2	—	—	23,7±4,2
3	—	—	62,9±8,5
4	IIIa	10	120±4,5
5	IIIb	10	137,6±3,4
6	IIIa	10	134,7±7,6
7	IIIa	1	157,1±10,4
8	IIIb	10	144,3±8,8
9	IIIb	1	130,6±13,5

*All animals other than those of the first group were ovariectomized. Groups 1 and 2 were the intact and ovariectomized controls respectively, the animals in groups 3 and 6-9 receiving estradiol in a dose of 50 μg/kg.
**In all cases except groups 8 and 9 (with respect to group 5) the differences in the factors were statistically significant.

phenol (IV), an intermediate in the synthesis of tamoxifen [6]. Debenzylation of (III) under these conditions did not result in isomerization, the ratio of Z- and E-isomers remaining the same as in the starting butene.

Compound (III) is an unreported analog of tamoxifen, and it was therefore of interest to examine the estrogenic and antiestrogenic activity of its isomers. It was not possible to isolate the E-isomer of (III) in the pure state, so that the Z-isomer (IIIa) and the compound (IIIb), which is a mixture of isomers in a ratio of 1:1, were examined. The latter was obtained by isometrizing (IV) in propan-2-ol in the presence of hydrochloric acid until the isomer ratio was 1:1, followed by benzylation of (IV) with benzyl chloride as decribed for the preparation of (I).

EXPERIMENTAL (CHEMISTRY)

The mass spectra of the compounds were obtained on a Varian MAT-112 instrument (West Germany), ionizing electron energy 70 eV, PMR spectra on a Varian XL-200 (Switzerland), internal standard tetramethylsilane, and IR spectra on a Perkin-Elmer 599 in Vaseline grease.* Chromatography was carried out on Silufol UV-254 plates (Czech SSR) in the system hexane—(2:1), developed with a 1% solution of vanillin in 10% perchloric acid.

1-Benzyloxy-4-(1,2-diphenylbut-1-enyl)benzene (III). To 47 ml of dry tetrahydrofuran was added under argon with stirring and cooling 5 ml (8.63 g, 0.045 mole) of $TiCl_4$, and to the bright yellow suspension was added portionwise 6 g (0.091 g-atom) of zinc dust at 25-30°C, and the mixture boiled for 1.5 h. After cooling, a solution of 4.34 g (0.015 mole) of 4-benzyloxybenzophenone (I) and 2 g (0.015 mole) of propiophenone (II) in 20 ml of tetrahydrofuran was added, and the mixture boiled for 0.5 h, until the ketone (I) was no longer present (TLC). After cooling to room temperature, the mixture was treated with 200 ml of 10% aqueous potassium carbonate, and extracted with ethyl acetate. The ethyl acetate extract was washed with water, evaporated to dryness, and the residue boiled with 15 ml of methanol. After cooling to 0°C, the solid was filtered off, washed with methanol, and dried to give 5.11 g (86.9% on 4-benzyloxybenzophenone) of the butene (III), mp 108-110°C. Mass spectrum: 390 (M^+), 299 ($M^+-C_6H_5CH_2$, 91 ($^+CH_2C_6H_5$). IR spectrum, ν_{max}: 1610 cm^{-1}. PMR spectrum (d-acetone), δ, ppm: 0.904 and 0.927 (3H, t, CH_3), 2.44 and 2.51 (2H, q, CH_2), 4.96 and 4.98 (2H, s, CH_2), ratio of Z/E isomers 5:1, 6.65-7.44 (arom. protons). Two recrystallizations from acetonitrile and alcohol gave the Z-isomer (IIIa), mp 122-126°C, R_f, 0.69. Its mass and IR spectra were

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identical with those given above. The PMR spectrum showed signals at 0.904, 2.44, 4.96, and in the region 6.65-7.44 ppm. $C_{29}H_{26}O$.

The combined mother liquors contained (by TLC) (V) (R_f 0.53), (VI) (R_f 0.47), and (VII) (R_f 0.91).

4-(1,2-Diphenylbut-1-enyl)phenol (IV). A mixture of 5 g (0.0128 mole) of (III) (Z/E 5:1) and 20 g of Raney nickel was boiled for 1 h. The catalyst was filtered off, the solution evaporated to dryness, and the residue triturated with hexane to give 3.27 g of the phenol (IV), mp 108-112°C (Z/E 5.3:1 by PMR), identical by TLC and in its mass spectrum with an authentic sample.

A mixture of 0.5 g of the butene (III) in 10 ml of 2-propanol with 15 ml of acetic acid and 15 ml of 40% HBr was boiled for 3 h. The 2-propanol was distilled off, and the oil extracted with petroleum ether (bp 40-60°C). The extract was boiled with charcoal, the charcoal filtered off, the filtrate concentrated to a small volume, cooled to 0°C, and the solid filtered off to give 0.2 g (52.6%) of (IV), mp 105-106°C, identical with an authentic sample.

1,2-Bis-(4-benzyloxyphenyl)-1,2-diphenylethylene (V). The low-valent titanium reagent was prepared as described above. To this reagent was added dropwise at 30°C a solution of 12 g (0.041 mole) of the ketone (I) in 50 ml of tetrahydrofuran, and the mixture boiled for 30 min, until all the starting material had been consumed (TLC). Workup of the reaction mixture as described above gave a partially crystalline solid, which was triturated with ether, filtered off, and recrystallized from acetonitrile to give 6.93 g [41.4% calculated on (I)] of product, mp 173-175°C, R_f 0.53. IR spectrum, ν_{max}: 1600 cm^{-1} (weak). Mass spectrum: 3544 (M^+), 453 ($M^+-C_6H_5CH_2$), 91 ($^+CH_2C_6H_5$). PMR spectrum ($CDCl_3$), δ, ppm: 4.96 and 4.98 (2H, s, CH_2). $C_{40}H_{32}O_2$.

EXPERIMENTAL (BIOLOGY)

The test compounds (IIIa) and (IIIb) were administered internally in vegetable oil, daily, once a day. Estrogenic activity was assessed by the stimulation of cornification of the vaginal epitheloum 48 h following 1-, 7-, and 15-day administration of (IIIa) and (IIIb) to ovariectomized mongrel female white rats, and uterotropic activity from the changes in weight of the rat uterus 48 h after 15 daily doses. Antiestrogenic activity was assessed by the ability to inhibit the uterotropic activity of estradiol (given daily in a dose of 50 μg/kg) in ovariectomized rats.

The test results are shown in Table 1, from which it will be seen that both (IIIa) and (IIIb) display considerable uterotropic activity, exceeding that of estradiol. Such increases in the mass of the uterus indicate that in both cases the bonding of the compounds with the estrogen receptors (ER) of the uterus is estrogenic rather than antiestrogenic [5]. The absence of high antiestrogenic activity (or the clear predominance of estrogenic over antiestrogenic activity in the case of (IIIb) is also shown by the observation that in both instances there was no decrease in uterine mass when the compounds were given in conjunction with estradiol. However, although when (IIIa) was given in conjunction with estradiol, there was a significant increase in uterine mass as compared with that in rate receiving (IIIa) only, when (IIIb) was given in conjunction with estradiol this effect was not seen. This could be due to the extended nuclear retention of the ER–compound complex in the nucleus as a result of the presence of the antiestrogenic E-isomer, and the definite refractory response to estradiol as a result of the absence of free cytoplastic ER [8].

At all times of examination, the vaginal smears showed a pronounced estrous reaction.

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